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autoclaving; narrow range of organ uptake for purposes of imaging; side-effects at doses in vast excess, for example, 100mg/kg body weight; restriction of use to either first pass or equilibrium dosing, and others that are described herein. Agents that overcome these problems, and that combine the properties of these two types of contrast agents, are highly desirable.

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Please replace Table 1 beginning on page 2, line 1 with the following rewritten Table 1:

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Table 1. Comparison of ideal properties of MRI contrast agents with properties of low molecular weight gadolinium based contrast agents and colloidal iron oxides.

| Properties of an ideal contrast agent | low molecular weight gadolinium | colloidal iron oxides |
|---|---------------------------------|-----------------------|
| Low production costs: efficient synthesis | Yes | No |
| Autoclavable without excipients | Yes | No |
| T1 agent | Yes | Sometimes |
| T2 agent | No | Yes |
| Non toxic at vast excess | Yes | No |
| Imaging vascular compartment at early phase (as a bolus administration) and at a late stage (equilibrium phase) | No | No |
| Multiple administration in single examination | No | No |
| Image of multiple target organs | Yes | Sometimes |
| Bolus injection | Yes | No |
| Low volume of injection | No | No |
| Iron source for anemia | No | Yes |

Please replace the paragraph beginning on page 3, line 12, with the following rewritten paragraph:

A3
In yet another embodiment, the invention provides a method of formulating an iron oxide complex coated with a reduced polysaccharide. This composition is for pharmacological use and the composition has decreased toxicity in comparison to an analogous iron oxide complex coated with native polysaccharide. The method of formulating such an iron oxide complex comprises: producing a reduced polysaccharide iron oxide complex, and sterilizing the complex by autoclaving. The formulation provides polysaccharide which was produced by reacting the polysaccharide with one of a reducing agent selected from the group consisting of a borohydride salt or hydrogen in the presence of an hydrogenation catalyst. The reduced polysaccharide iron oxide complex has such decreased toxicity. In a further aspect of the method, the iron oxide is superparamagnetic.

Please replace the paragraph beginning on page 11, line 14, with the following rewritten paragraph:

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Methods of preventing clumping of the colloid induced by heat stress that have no effect on coating dissociation have also been described. These methods generally include the use of excipients during the autoclaving process. Groman et al., U.S. Patent 4,827,945, and Lewis et al., U.S. Patent 5,055,288, both patents hereby incorporated herein by reference, use citrate to prevent clumping of the particles when the coating dissociates. Groman et al., U.S. Patent 5,102,652, hereby incorporated herein by reference, uses low molecular weight carbohydrates such as mannitol to prevent clumping during autoclaving. These excipients increase the cost and complexity of manufacturing the product, yet do not solve the problem of dissociation of the polymer from the iron particle.

Please replace the paragraph beginning on page 12, line 25, with the following rewritten paragraph:

A^b A dextran can elicit a sometimes fatal anaphylactic response when administered intravenously (i.v.) in man (Briseid, G. et al., *Acta Pharmcol. Et Toxicol.*, 1980, 47:119-126; Hedin, H. et al., *Int. Arch. Allergy and Immunol.*, 1997;113:358-359). Related adverse reactions have been observed also on administration of magnetic dextran coated iron oxide colloids. Non-magnetic dextran coated iron oxide colloids that have utility as hematinics, particularly as an adjunct to erythropoietin treatment for end stage renal dialysis patients, may have side effects.

Please replace the paragraph beginning on page 16, line 4, with the following rewritten paragraph:

A^b The term "colloid" as used in this specification and the accompanying claims shall include any macromolecule or particle having a size less than about 250 nm. The iron oxide polysaccharide colloids of the invention have substantially improved physical characteristics and manufacturability compared to previously described materials. Improved physical characteristics are evident in the ability of the colloid to withstand heat stress, as measured by subjecting the colloid to a temperature of 121°C for 30 minutes. Colloid particles made according to the invention show less evidence of polysaccharide dissociation under stress, remaining colloidal, and exhibiting no appreciable change in size.

Please replace the paragraph beginning on page 17, line 3, with the following rewritten paragraph:

A7 The colloids that are an embodiment of the invention can be used as contrast agents for magnetic resonance imaging (MRI) or in other applications such as magnetic fractionation of cells, immunoassays, magnetically targeted drug delivery, and as therapeutic injectable iron supplements. These colloids are particularly suited to parenteral administration, because the final sterilization typically is autoclaving, a preferred method since it eliminates viability of all cellular life forms including bacterial spores, and viruses. Previous methods for making colloids required the addition of excipients such as citrate or low molecular weight polysaccharides as stabilizers during the autoclaving process (see U.S. Patent 4,827,945 and U.S. Patent 5,102,652), or avoided heat stress altogether by use of filter sterilization (see U.S. Patent 5,150,726). Thus, the embodiments of the present invention comprising the colloid compositions, provide utilities as significantly improved MRI contrast agents, and hematinic agents that are iron supplements. The improvements provided in these agents over prior art are found in the following facts demonstrated in the examples herein: that the agents which are embodiments of the present invention are heat sterilizable by autoclaving, and are thus optimized for long-term storage at ambient temperatures; that these agents do not require the addition of excipients for maintenance of stability during the sterilization or storage processes; that the agents are non-toxic to mammals including humans at higher doses; that an effective dose of the agents used for imaging is a smaller amount of material than the agents described in the art; and that the pharmacokinetics following administration are such that iterated successive doses administered after a brief interval after administration of a first dose can be used to obtain additional images during a single clinical visit and use of the imaging apparatus.

Please replace the paragraph beginning on page 19, line 22, with the following rewritten paragraph:

A8 In Examples 52-53, the presence of symptoms of toxicity to rats at doses in vast excess of reduced and non-reduced (native) dextran coated USPIOs was determined, with response to an anaphylactic type reaction. The extent of the anaphylactic type reaction is determined by volume of paw edema. Similar studies were performed using native, reduced, and carboxymethylated reduced dextrans. The results are summarized Tables 11-14.

Please replace the paragraph beginning on page 45, line 21, with the following rewritten paragraph:

A9 Example 52. Toxicity studies in rats. Toxicity of reduced dextran, non-reduced dextran, and CMRD coated colloids administered in vast excess to rats.

Please replace the paragraph beginning on page 51, line 18, with the following rewritten paragraph:

A10 No adverse reactions attributable to administration of the composition were observed among the treated subjects at any dose, including the highest doses (4mg/kg).